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Clinical Comparison of Intramuscular Terbutaline and Subcutaneous Adrenaline in Bronchial Asthma

S. Johansen

Laboratory of Clinical Allergology, Department IX, Ullevål Hospital, University Clinic, Oslo, Norway

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Summary. In a double-blind cross-over trial in 20 asthmatic patients, terbutaline 0.25 mg i.m. was compared with adrenaline 0.3 mg given subcutaneously. Both drugs caused pronounced bronchodilatation after 5 minutes and a maximal effect after 60 min. There was no significant difference in onset or duration of their actions. Adrenaline had a slightly greater maximum effect ($p < 0.05$), there was a slight rise in heart rate and a signficant fall in diastolic blood pressure after terbutaline, and a slight decrease in heart rate after adrenaline. Side effects occurred in 6 patients after adrenaline and 7 after terbutaline, the most important being slight tremor and restlessness. Intramuscular terbutaline is an effective alternative to the established use of adrenaline in the treatment of bronchial asthma.

Key words. Terbutaline, adrenaline, intramuscular injection, bronchodilatation, asthma.

Sympathomimetic amines have been used in the treatment of bronchial asthma since Barger and Dale [1] introduced adrenaline in 1910, despite their disadvantage of an concomitant but undesirable effect on the heart. An important advance was when Lands *et al.* showed that the adrenergic beta-receptors in the heart and the bronchi were not identical, and distinguished them as β_1- and β_2-receptors, respectively [2]. Terbutaline (Bricanyl®; Draco, a subsidiary of AB Astra, Sweden) is a new sympathomimetic amine, which has been shown in animal experiments to have marked specificity for bronchial β_2-receptors [3]. It differs chemically from adrenaline by having a tertiary butyl group on the nitrogen atom instead of a methyl group, and the hydroxyl groups in the meta position in the benzene ring (Fig. 1). Satisfactory relief of bronchial obstruction in asthmatic patients has been reported following its subcutaneous injection, oral administration or aerosol inhalation [4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14]. There have only been a few preliminary experiments in normal human subjects [15] to demonstrate the effects of intramuscular administration of terbutaline. The aim of the present study was to compare the actions and side effects in asthmatic patients of terbutaline given intramuscularly, and adrenaline given subcutaneously.

Materials and Methods

20 patients (4 in-patients and 16 out-patients) with reversible bronchial obstruction were studied; their clinical details have been summarized in Table 1. None of the patients suffered from cardiac disease. The diagnosis of extrinsic asthma was based on bronchial provocation tests. The study was designed as a double-blind cross-over trial covering two consecutive days, and, as far as possible, recordings were begun at the same time on each morning. All broncholytic drugs were withdrawn at least 6 h before each day's experiment; treatment with

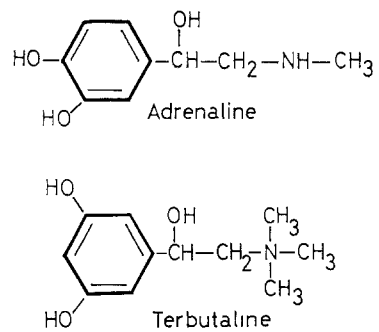

Fig. 1. Structural formulae of adrenaline and terbutaline

corticosteroids (prednisone), antibiotics and other regular therapy was kept unchanged during the study. Terbutaline and adrenaline were administered in doses of 0.25 mg i.m. and 0.3 mg s.c., respectively. The order of drug administration was randomized, and identical ampoules containing 1 ml of terbutaline, adrenaline or placebo were used. On each day two injections of 0.5 ml were given successively within 20 sec, the first subcutaneously in the upper arm, and the second intramuscularly in the gluteal

region. On the day that terbutaline was given, the subcutaneous injection contained placebo, and the day adrenaline was administered, the intramuscular injection contained placebo.

Broncholytic response, heart rate, and blood pressure were assessed before and at intervals of 5, 15, 30, 45, 60, 120, and 180 min after treatment.

Broncholytic response was measured as forced expiratory volume in the first second ($FEV_{1.0}$) with a Vitalograph® dry spirometer, the patient being upright. At each time interval two measurements were made, and the highest value was used in the calculations. To obtain pretreatment values, each day's experiment started with a 5 min rest in the sitting position. Then, recordings were made at 5—10 min intervals until consecutive $FEV_{1.0}$-values were unchanged or began to decrease. The final pretreatment values were used to evaluate response to the drug. The means of the absolute changes in $FEV_{1.0}$ at each time interval were calculated for each drug.

Heart rate and blood pressure were assessed just before spirometry with the patient sitting. The means of the absolute changes in heart rate and systolic and diastolic pressure at each time interval were calculated for each drug. Side effects were also recorded. Spontaneous comments about discomfort were noted and each day, at the end of the experiment, patients were asked: "Did you notice any discomfort after the injections?" Student's t-test for paired comparisons was used for statistical analysis.

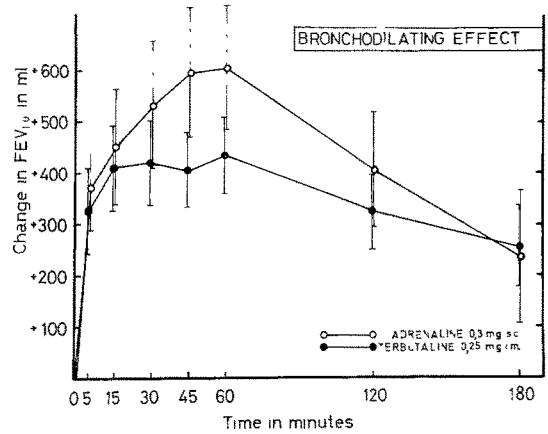

Fig. 2. Bronchodilator effect of terbutaline 0.25 mg i.m. and adrenaline 0.3 mg s.c. Mean change in Forced Expiratory Volume (FEV_1, ml) in 20 patients at intervals after treatment. Initial values: Terbutaline 1210 ml, Adrenaline 1320 ml

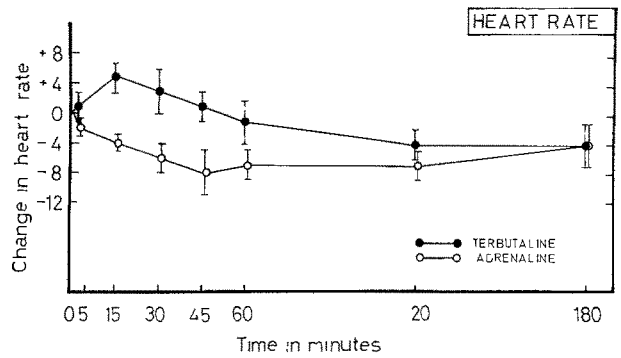

Fig. 3. Effect on heart rate (beats/minute) of terbutaline 0.25 mg i.m. and adrenaline 0.3 mg s.c. Mean changes in 20 patients at intervals after treatment. Initial values: Terbutaline 90.4 beats/min, Adrenaline 88.6 beats/min

Results

Bronchodilator Effect

The mean absolute changes in $FEV_{1.0}$ at each interval for each drug are shown in Fig. 2. Both drugs produced rapid, pronounced bronchodilatation, and a highly significant increase in $FEV_{1.0}$ after 5 min. The maximum effects of both drugs were reached after 60 min. There was no signficant difference between the drugs in speed of onset or duration of action, but adrenaline had a somewhat greater effect, being just significant ($p < 0.05$).

The clinical condition of two patients deteriorated between 120 and 180 min after terbutaline and they required additional broncholytic therapy. In these two cases $FEV_{1.0}$ values recorded at 120 min have been used for calculation and comparison of the means at 180 min, and this has also been done for their heart rates and blood pressures. It seems highly unlikely that this had any particular effect on the results.

Heart Rate and Blood Pressure

Terbutaline increased the heart rate by about 5 beats/min, whereas adrenaline caused a decrease (Fig. 3). A highly significant difference between the drugs was noted after 15 and 45 min ($p < 0.001$).

Both drugs caused a slight fall in systolic blood pressure (Fig. 4). After terbutaline there was a highly significant decrease in diastolic pressure (Fig. 4), but only a slight decrease occurred after adrenaline. The difference between the drugs was significant ($p < 0.01$).

Side Effects

Side effects were noted in 7 patients after terbutaline and after adrenaline in 6; in 4 patients they occurred after both drugs; in 2 after adrenaline only; and, in 3, after terbutaline alone. The most important was a subjective feeling of slight tremor

or restlessness after terbutaline in 5 patients, and adrenaline in 4. Patients who had side effects were younger than the others, the mean ages being 37.1 and 47.3 years, respectively (excluding the patient who was taking Sarotex). This difference was significant according to Wilcoxon's rank test ($p < 0.01$).

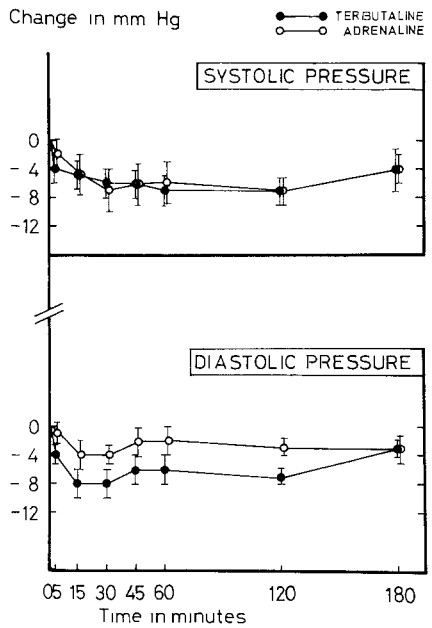

Fig. 4. Effects on blood pressure of terbutaline 0.25 mg i.m. and adrenaline 0.3 mg s.c. Mean changes in 20 patients at intervals after treatment.

Initial values	Systolic	Diastolic
Terbutaline	128 mm Hg	87 mm Hg
Adrenaline	127 mm Hg	85 mm Hg

Discussion

In clinical trials of bronchodilators, patients must be in a state of reversible bronchial obstruction. It is also necessary to ensure minimal differences in the pretreatment values for each drug, because the response to a bronchodilator may be less when obstruction is mild than when it is severe. At the time of the experiment the present patients had pretreatment values markedly lower than their maximal $FEV_{1\,0}$ recorded during the preceding year (Table 1). The differences between pretreatment values was small in the majority of the patients. The mean pretreatment values of $FEV_{1\,0}$ before terbutaline and adrenaline differed by only 100 ml, except in 5, in whom there were marked differences. However, exclusion of these patients from the statistical analysis did not affect the results. The reproducibility of the spirometric method employed, seemed satisfactory as there were only small variations in $FEV_{1\,0}$ between the two attempts at each time interval; see, for example, the almost identical first and second values of $FEV_{1\,0}$ in 20 patients before terbutaline shown in Table 2.

Terbutaline i.m. has been shown here to produce rapid and pronounced bronchodiltation; the average increase in $FEV_{1.0}$ after 5 min was 320 ml, which was about 75% of the maximum improvement. The onset of action was almost the same as for adrenaline. An earlier report comparing subcutaneous doses, suggested that terbutaline had a faster onset of action than adrenaline [10], but this was not confirmed in another study by Nou [14]. In the present study, the maximum effect of adrenaline was somewhat greater than that of terbutaline, in agreement with the findings of Verstraeten [10], but in direct contradiction to the results of Nou, who reported that terbutaline was more effective [14]. No significant difference in the duration of action has been noted in any of these studies. As there are different opinions about the onset of action and maximum bronchodilator effect of terbutaline and adrenaline, further studies of the subject appear justified, including the comparison of subcutaneous and intramuscular doses of terbutaline. Dose-response studies of i.m. terbutaline should also be done, as 0.375 mg or 0.5 mg might have even greater effects.

The tachycardia reported previously after terbutaline given subcutaneously or by mouth [5, 8, 9, 10, 11, 12, 14, 15, 16] has been confirmed, but it was so small that it was only of minor clinical importance. The difference between the effects of terbutaline and adrenaline on heart rate was remarkable, but its cause is not known. It is possible that it was due to the difference observed in the bronchodilator effect, and it has also been suggested that clinical doses of terbutaline may have some effect on beta-1 receptors [8, 9]. Another possibility would be that the tachycardia was in part a baroreceptor-induced reflex in response to peripheral vasodilatation [6]. The rise in heart rate is of great importance, as the claim to superiority of the new sympathomimetic amines has been based on the selectivity of their bronchodilator effects.

The side effects produced by i.m. terbutaline in the present study were the same as those reported earlier to follow its oral and subcutaneous administration, and their frequency was also similar to that found after subcutaneous doses. In the present study, both drugs were injected rapidly unlike the majority of other clinical trials in which they have been given slowly, e.g. a dose subcutaneously in 5 min, because of the risk of the cardiovascular side effects of adrenaline.

Table 1. *Clinical details of the patients*

Case No.	Sex	Age (years)	Type of asthma	Blood eosinophilia (>400)	Chronic bronchitis	Duration of asthma (years)	Longterm corticosteroids	FEV_1-max last year	FEV_1-pretreatment value A*	T*	Other diseases
1	M	69	Intrinsic	+	+	5–10	+	3050	950	650	
2	F	48	Intrinsic	+	+	5–10	+	1850	1150	2100	
3	M	24	Intrinsic	+		>10		3500	1600	2100	
4	F	37	Intrinsic		+	< 5		1400	800	700	
5	F	34	Intrinsic	+		< 5		1900	1750	1500	
6	M	39	Intrinsic		+	>10		1900	1450	1250	
7	M	50	Intrinsic			>10	+	1500	750	750	
8	M	58	Intrinsic		+	>10		1350	950	650	
9	M	44	Intrinsic	+	+	< 5	+	2800	750	700	
10	F	27	Intrinsic		+	< 5		3500	750	650	
11	M	40	Intrinsic		+	< 5		1500	1000	950	Chronic alcoholism.
12	M	52	Extrinsic		+	< 5		2500	1250	900	
13	M	58	?			< 5		3050	1400	2050	Depression (Sarotex® and Librium®).
14	F	61	Intrinsic	+	+	5–10	+	2050	1250	1300	
15	M	48	Intrinsic			>10	+	4000	1500	1050	
16	F	25	Extrinsic			>10		2100	700	1350	Allergic rhinoconjunctivitis.
17	M	52	Extrinsic		+	>10		2900	1550	1400	
18	F	22	Extrinsic			>10		3050	2100	2200	
19	M	30	Extrinsic		+	>10	+	1750	1200	550	
20	M	20	Extrinsic	+		< 5		4500	3500	1450	Allergic rhino conjunctivitis.

* A = Adrenaline
* T = Terbutaline

Table 2. *FEV_1 (ml) at first and second attempts before terbutaline*

Case No.	First measurement	Second measurement
1	650	650
2	2100	2100
3	2100	1950
4	700	700
5	1500	1500
6	1250	1200
7	750	750
8	650	650
9	700	600
10	650	500
11	800	950
12	900	900
13	1950	2050
14	1300	1300
15	950	1050
16	1350	1350
17	1350	1400
18	2200	2100
19	550	450
20	1300	1450
M	1185.0	1180.0
S	546.8	550.9
SEM	122.3	123.2
t_0	0.26	

In conclusion, terbutaline, 0.25 mg injected intramuscularly caused pronounced bronchodilatation after 5 min and so did adrenaline 0.3 mg given subcutaneously. The latter had a slightly greater maximum effect. Unlike adrenaline, which lowered the heart rate, terbutaline produced slight tachycardia. The type and frequency of side effects were the same for both drugs. Intramuscular administration of terbutaline appears to be a suitable alternative to the established use of adrenaline in the treatment of bronchial asthma.

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Dr. S. Johansen
Medical Department A
Aker Hospital
Oslo
Norway